14. (Amended) The method of claim 1, wherein said second chimeric protein is a protein transported into said cell.

In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

REMARKS

The Status of the Claims.

Claims 1-20 are pending with entry of this amendment, claims 21 and 94 being cancelled. Claims 1, 9 and 14 are amended herein. These amendments introduce no new matter and support is replete throughout the specification.

With respect to claim 1, support for "wherein said mammalian cell comprises a degradation deficiency of the metabolic product" can be found throughout the specification. For example, see specification at page 24, 2nd full paragraph (starting with "Instead") to page 25, end of 2nd full paragraph (starting with "The methods"), at page 26, last paragraph (starting with "In the case"), at page 33, 4th paragraph (starting with "Virtually") to page 34, end of 2nd full paragraph (starting with "Depending"), at page 46, 2nd full paragraph (starting with "Accumulation"), page 48, 1st full paragraph (starting with "All"), at page 50, 2nd full paragraph (starting with "We"), at page 51, 1st and 2nd full paragraph (starting with "As" and "In", respectively), at page 52, 1st full paragraph and 3rd paragraph, which continues to page 53 (starting with "As" and "In", respectively). Claim 1 is also amended to remove "first" before nucleic acid. Applicants cancel claim 21 in this amendment, therefore the "first" is no longer needed in the claim. Claims 9 and 14 are amended to clarify antecedent basis and to correct a typographical error. Support for the amendment to correct the typographical error is found throughout the specification, e.g., at page 4, 1st full paragraph (starting with "The").

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Drawings.

Applicants note that the corrected drawing of Figure 1 filed on 11 June 2002 has been approved by the Examiner. Action at page 2. Applicants submit herewith a Letter to the Draftperson with Formal Drawings.

Request for Continued Examination

Applicants file herewith a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on August 22, 2002. In the Action, the Examiner indicated that the reference 24 was a duplicate. Applicants note that the reference appears on PTO-892, which is a part of Paper No. 9, mailed December 4, 2001. Applicants note that the first author of the paper is "Nagahara et al.", not "Hagahara et al." as indicated in the PTO-892 form.

Applicants submit herewith a supplemental Information Disclosure Statement (Form 1449), which contains the references from the international search report that have not been previously submitted along with a copy of the international search report.

35 U.S.C. §112, Second Paragraph.

Claim 21

Claim 21 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because "it is [allegedly] unclear what the nexus is between the second nucleic acid (which encodes only the ligand or metabolic product and not the chimeric protein comprising the ligand or metabolic product) and the other steps of the methods." Action at page 2 and 3. Applicants have canceled claim 21, rendering the rejection moot.

Claim 94

Claim 94 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because "[i]t is [allegedly] unclear if the metabolic product accumulates with respect to the

presence or the absence of the agent being screened in the method of claim 1." Action at page 6. Applicants have canceled claim 94. Accordingly, the rejection with respect to claim 94 is moot.

35 U.S.C. §102.

Claims 1, 2, 6, 10-12, and 94 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Karin et al. (US Pat. No.: 6,242,253) ("Karin"). Action at page 2 and 4. To the extent that the rejection is applied to the amended claims, Applicants traverse.

With respect to claim 1 (and its dependent claims 2, 6, and 10-12), in order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983). Amended claim 1 recites a "metabolic product," "a mammalian cell," and "wherein said mammalian cell comprises a degradation deficiency of the metabolic product." These limitations are also incorporated into the dependent claims.

Beta-catenin (which is recited in dependent claim 10) is one example of a metabolic product that is degraded in an APC-dependent manner. Normal cells have a functional APC, which immediately degrades beta-catenin. However, beta-catenin accumulates in cells with certain mutant APCs, e.g., in SW480 cells, because these mutant APC lose the ability to degrade beta-catenin. *See* specification, e.g., at page 46-54.

Even if one were to apply a two-hybrid assay in a cell that does not comprise a degradation deficiency of a metabolic product, the "metabolic product" will be degraded immediately and it is very likely that the two-hybrid assay would not function. In this situation, screening for an agent that modulates the amount of metabolic products would be impossible.

The limitations of amended claim 1 are not found in Karin. Karin basically focuses on the IKK gene and not the two-hybrid assay. Karin refers to methods to identify an agent that modulates association between IKK and its interacting protein, and a two-hybrid assay, e.g., at column 19, line 42, to column 24, line 59, and at column 25, line 23 to line 60 in Karin. However, they are general descriptions of a yeast two-hybrid assay. Moreover, it neither mentions nor suggests the screening method of claim 1, which recites "a mammalian cell" and "wherein said mammalian cell comprises a degradation deficiency of the metabolic product." Thus, Karin fails to disclose each and every limitation of the claimed invention. Accordingly, the rejection with respect

to amended claim 1 (and its dependent claims 2, 6, and 10-12) under 35 U.S.C. §102(e) should be withdrawn. Applicants have canceled claim 94, therefore the rejection with respect to this claim is moot.

35 U.S.C. §103(a).

Claims 1-12, 19-21 and 94

Claims 1-12, 19-21, and 94 were rejected under 35 U.S.C. §103(a) as allegedly being obvious in light of Karin as applied to claims 1, 2, 6, 10-12 and 94 and further in view of Sadowski et al., (US Pat. No.: 5,885,779) ("Sadowski"), Young (Biology of Reproduction (1998) 58:302-311) ("Young") and Finley et al., (in The Yeast Two-Hybrid System, eds P. Bartel, S. Fields, Oxford University Press, (1997) pp. 197-214) ("Finley"). Action at page 2-3 and 4-5. To the extent that the rejection is applied to the amended claims, Applicants traverse.

Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As discussed above, Karin fails to disclose each and every limitation of independent amended claim 1 (and its dependent claims 2-12, and 19-20). This deficiency is not remedied by Sadowski, Young, and Finley. Sadowski, Young and/or Finley, alone or in combination, do not disclose the limitations of amended claim 1 (and its dependent claims 2-12, and 19-20). Sadowski discloses a system for assaying protein-protein interactions using a repressed transactivator system, such as transcriptional repressor proteins. Sadowski fails to disclose a mammalian cell, which comprises a degradation deficiency of a metabolic product, which is recited in amended claim 1 (and its dependent claims). Young and/or Finley also fail to remedy the deficiency. Both Young and Finley teach general aspects of two-hybrid assay. Young and/or Finley fail to disclose a screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product in a mammalian cell, where the mammalian cell comprises a degradation deficiency of the metabolic

product. As a result, the rejection fails to establish the first requirement for establishing a *prima facie* case of obviousness.

Karin also does not provide teaching, suggestion or motivation to combine this reference with others to provide Applicants' invention and fails to provide a reasonable expectation of success of obtaining Applicants' invention, which are also required to establish a *prima facie* case of obviousness. Thus, the rejection with respect to 1-12, and 19-20 claims under 35 U.S.C. §103(a) should be withdrawn. Claims 21 and 94 have been canceled, thus the rejection with respect to these claims is moot.

Claims 1-21

Claims 1-21 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Barker et al. (US Pat. No.: 5,851,775) ("Barker") and in view of Sadowski, Young, Finley, Nagahara et al (Nature Medicine (1998) 4:1449-1452) ("Nagahara") and Schwarze et al. (Science (1999) 285:1569-1572) ("Schwarze"). Action at page 3 and 5-6. As the rejection applies to the rejected claims, Applicants traverse.

The requirements for a *prima facie* case of obviousness are set forth above.

Barker, Sadowski, Young, Finley, Nagahara, and Schwarze, alone or in combination, fail to provide all the elements of the claimed invention. At most, Barker relates to a screening method that consists of a reporter assay using a Tcf-responsive reporter gene (where the Tcf-responsive reporter gene must be introduced into the cell), for an agent effective on APC related diseases. *See, e.g.,* Barker at column 6, lines 35-36. Barker indicates that a two-hybrid assay can be used to identify an agent that inhibits interaction between beta-catenin and Tcf-4. See column, 6, line 45-line 55. However, Barker does not disclose using a mammalian two-hybrid system and does not disclose any details of how a two-hybrid system is to be applied to the task at hand. Barker also completely fails to disclose a two-hybrid system in a mammalian cell, where the mammalian cell comprises a degradation deficiency of the metabolic product, as recited in independent claim 1 (and its dependent claims 2-20). At the time of filing the application, the mammalian two-hybrid assay was not in common use. After repeated experiments by the inventors, the claimed invention was developed in mammalian cells. This work was published in Cancer Research, *A mammalian two-hybrid system for adeomatous polyposis coli-mutated colon cancer therapeutics*, (2001) 61, 3: 854-858. Furthermore, the benefit of using mammalian cells and not yeast for this assay was to obtain

protein modifications that occur in mammalian cells and not in yeast cells---an advantage not recognized in the cited art.

Barker's deficiency is not remedied by Sadowski, Young, Finley, Nagahara, and/or Schwarze, alone or in combination. As indicated above, Sadowski, Young and/or Finley do not remedy the deficiency of Barker. Sadowski discloses a system for assaying protein-protein interactions using a repressed transactivator system, such as transcriptional repressor proteins. Both Young and Finley teach general aspects of two-hybrid assay. These references do not disclose a two-hybrid system in a mammalian cell, where the mammalian cell comprises a degradation deficiency of the metabolic product, as recited in independent claim 1 (and its dependent claims 2-20)

Nagahara and/or Schwarze, alone or in combination, also do not remedy the deficiency of Barker, Sadowski, Young, and/or Finley. Nagahara and Schwarze pertain to the use of a human immunodeficiency virus TAT protein to transduce proteins into target cells. Nagahara and/or Schwarze do not teach or suggest a two hybrid system, a two hybrid system in mammalian cells, or of methods of screening for modulators of the ability of a mammalian cell to accumulate or to degrade a metabolic product, where the mammalian cell comprises a degradation deficiency of the metabolic product. Thus, all the limitations of the claimed invention are not provided by the references, alone or in combination. As a result, the first requirement for establishing a *prima facie* case of obviousness is not met.

Barker also does not provide teaching, suggestion or motivation to combine the teachings of the reference with the other cited references and fails to provide a reasonable expectation of success of obtaining Applicants' invention, which are also required to establish a *prima facie* case of obviousness. Thus, the rejection of claims 1-20 under 35 U.S.C. § 103(a) should be withdrawn. Claims 21 and 94 have been canceled; thus, the rejection with respect to these claims is moot.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/687,593 WITH ENTRY OF THIS AMENDMENT

1. (~~Previously~~ Twice amended) A method of screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said method comprising:

(i) providing a mammalian cell comprising:

a ~~first~~ nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding domain that binds said peptide binding site attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

(ii) contacting said cell with a test agent; and

(iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product,

wherein said mammalian cell comprises a degradation deficiency of the metabolic product.

9. (Amended~~Original~~) The method of claim ~~1~~6, wherein said apoptosis gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

14. (~~Original~~Amended) The method of claim 1, wherein said ~~first~~ second chimeric protein is a protein transported into said cell.

21. (~~Original~~Cancel) ~~The method of claim 1, wherein said cell further comprises a second nucleic acid encoding said ligand or metabolic product operably linked to an inducible promoter.~~

94. (~~Previously Added~~Cancel) ~~The method of claim 1, wherein said metabolic product is a metabolic product that is accumulated by said cell.~~

APPENDIX B

CLAIMS PENDING IN USSN 09/687,593 WITH ENTRY OF THIS AMENDMENT

1. (Twice amended) A method of screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said method comprising:

(i) providing a mammalian cell comprising:

a nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding domain that binds said peptide binding site attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

(ii) contacting said cell with a test agent; and

(iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product,

wherein said mammalian cell comprises a degradation deficiency of the metabolic product.

2. (Original) The method of claim 1, wherein said expression control protein is a transactivator.

3. (Original) The method of claim 2, wherein said transactivator is VP16.

4. (Original) The method of claim 1, wherein said expression control protein is a repressor.

5. (Original) The method of claim 1, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

6. (Original) The method of claim 1, wherein said effector is selected from the group consisting of a reporter gene, a cytotoxin, and an apoptosis gene.

7. (Previously amended) The method of claim 1, wherein said effector comprises a reporter gene selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, beta -galactosidase (β-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

8. (Original) The method of claim 1, wherein said effector encodes a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

9. (Amended) The method of claim 6, wherein said apoptosis gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

10. (Previously Amended) The method of claim 1, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its receptor partner.

11. (Original) The method of claim 1, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

12. (Original) The method of claim 1, wherein said second chimeric protein is expressed from a nucleic acid in said cell.

13. (Original) The method of claim 1, wherein said first chimeric protein is a protein transported into said cell.

14. (Amended) The method of claim 1, wherein said second chimeric protein is a protein transported into said cell.

15. (Original) The method of claim 1, wherein said first chimeric protein or said second chimeric protein comprises an HIV TAT domain.

16. (Original) The method of claim 1, wherein said cell is a cell selected from the group consisting of SW480, SW48, DLD-1, HCT-116, HT29, 293, U-20S, T-47D, MCF-7, HeLa, A549, Hep G2, and a Jarkat cell.

17. (Original) The method of claim 1, wherein

said nucleic acid encodes a GAL-4 binding site, and said effector gene is a reporter gene;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

18. (Original) The method of claim 17, wherein said Tcf is Tcf4.

19. (Previously Amended) The method of claim 1, wherein said cell comprises a nucleic acid encoding said first or said second chimeric protein under control of a tissue specific or an inducible promoter.

20. (Original) The method of claim 19, wherein said promoter is an ecdysone promoter.

21-94. (Cancelled)